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INVITED ARTICLE

Right ventricular systolic echocardiographic parameters in chronic systolic heart failure and prognosis

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KEYWORDS

Heart failure;
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Abstract *Background:* Right ventricular (RV) dysfunction is associated with poor prognosis in patients with heart failure (HF). Several RV echocardiographic parameters have been proposed as sensitive markers to detect patients at risk.
Objective: The aim is to compare the predictive value of several RV systolic echocardiographic parameters for adverse outcome in patients with chronic systolic HF.
Methods: We assessed 117 patients with chronic systolic HF and left ventricular ejection fraction (LVEF) <40% for the following: (i) RV fractional area change (RVFAC), (ii) tricuspid annular plane systolic excursion (TAPSE), (iii) integral of the systolic wave (ISW_{tdi}), and (iv) peak systolic velocity (Sa_{tdi}). ISW_{tdi} and Sa_{tdi} were measured using tissue Doppler imaging at the tricuspid annulus. The primary endpoint was death, urgent transplantation, or acute HF episode requiring hospital admission. The follow-up extended for one year.
Results: Fifty-two patients reached the primary endpoint. The cut-off thresholds for RVFAC, TAPSE, Sa_{tdi}, and ISW_{tdi} defined using receiver-operating characteristic curves were 30%, 15.5 mm, 10.0 cm/s, and 2.4 cm, respectively. The area under the curve and the 95% confidence interval for RVFAC, TAPSE, Sa_{tdi}, and ISW_{tdi} were 0.71(0.65–0.85), 0.66(0.55–0.76), 0.85(0.70–0.96), and 0.75(0.64–0.86), respectively. NYHA > 2, and Sa_{tdi} were found to be independent predictors of adverse outcome.
Conclusion: Sa_{tdi} is an independent predictor of adverse outcome in HF at a threshold value of 10.0 cm/s and appears to be superior to other RV systolic echocardiographic parameters.

1. Introduction

Despite recent advances in diagnosis and treatment, patients with heart failure (HF) still have a poor prognosis.[1,2] It is, therefore, important to establish a reliable means of identifying those patients at a higher risk. Right ventricular (RV) systolic dysfunction (assessed with thermodilution, or radionuclide

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ventriculography) in patients with chronic HF is associated with poor long-term prognosis.[3–5] The RV ejection fraction (EF) predicts death, hospitalization and exercise capacity more accurately than the maximal oxygen consumption.[4]

Echocardiography is a non-invasive, inexpensive and readily available method of RV function assessment. However, precise echocardiographic assessment of RV systolic function is challenging, primarily because the morphology of RV is complicated. Recently, different echocardiographic parameters have been proposed for the assessment of RV systolic function,[6] including tricuspid annular plane systolic excursion (TAPSE) using M-mode,[7,8] tissue Doppler imaging (TDI) measuring the peak systolic velocity (Sa_{tdi}),[9] and the integral of the systolic wave (ISW_{tdi}) of the tricuspid annulus.[10] However, there is still discussion about the best echocardiographic parameters for predicting outcome in HF.

2. Objective

The aim is to compare the predictive value of several RV echocardiographic parameters for adverse outcome in patients with chronic systolic heart failure.

3. Methodology

3.1. Patient population

We enrolled 120 consecutive patients with chronic heart failure evaluated at a tertiary cardiac center from 2009 to 2011. Inclusion criteria were age > 18 years, symptomatic heart failure (New York Heart Association class II-IV), and left ventricular ejection fraction (LVEF) < 40%. Exclusion criteria were mitral stenosis, mitral valve surgery, severe mitral regurgitation (> grade 3), severe aortic stenosis (peak velocity > 4 m/s), severe tricuspid regurgitation, malignancy, and severe renal failure requiring dialysis. Detailed medical history and clinical examination were recorded for all patients. Patients underwent a detailed echocardiographic assessment within 24 h from presentation.

The study was approved by the medical ethics committee of our institution. The study protocol was designed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All patients gave informed consent before the procedure.

3.2. Echocardiographic examination

Comprehensive transthoracic echocardiography was performed using an Aloka alpha 5 echocardiography machine (Hitachi Aloka Medical, Ltd., manufactured in Tokyo, Japan) equipped with tissue Doppler imaging (TDI) technology. Two-dimensional, M-mode, Doppler echocardiography measurements and quantification were performed according to recommendations of the American Society of Echocardiography.[11,12] Continuous Doppler echocardiography was used to measure pulmonary artery and aortic velocities, tricuspid regurgitation velocity, and mitral regurgitation velocity. Pulsed Doppler echocardiography for the assessment of the standard diastolic

Table 1 Baseline demographic and clinical characteristics of the patients according to the incidence of primary outcome events.

Variables	Event		
	Yes (n = 52)	No (n = 65)	p value
Age (years)	54.5 ± 14.8	54 ± 14	> 0.05
Body surface area (m^2)	1.81 ± 0.4	1.85 ± 0.2	> 0.05
Systolic BP (mmHg)	120 ± 11	123 ± 12	> 0.05
Diastolic BP (mmHg)	79 ± 4	80.3 ± 6	> 0.05
Gender			
Male	42(80.8%)	45(69.2%)	> 0.05
Female	10(19.2%)	20(30.8%)	
Etiology of HF			
Ischemic	24(46.2%)	26(40%)	> 0.05
Non-ischemic	28(53.8%)	39(60%)	
NYHA class III–IV	50(96.2%)	39(60%)	< 0.001
Heart rate	87 ± 5	93 ± 20	> 0.05
Hypertension	10(19.2%)	14(21.9%)	> 0.05
Smoking	14(26.9%)	13(20%)	> 0.05
Diabetes	25(48.1%)	18(27.7%)	< 0.05
Previous myocardial infarction	19(36.5%)	19(29.2%	> 0.05
Previous HF admission	36(69.2%)	21(32.3%)	< 0.001
Previous PCI	3(5.8%)	2(3.1%)	> 0.05
Previous CABG	3(5.8%)	5(7.7%)	> 0.05
B-blockers	36(69.2%)	52(80%)	> 0.05
ACE-inhibitors	48(92.3%)	65(100%)	> 0.05
Diuretics	51(98.1%)	57(87.7%)	< 0.05
Digitalis	31(59.6%)	27(41.5%)	< 0.05
Spironolactone	36(69.2%)	32(49.2%)	< 0.05

Data are expressed as a mean ± standard deviation or a number (percent). BP = blood pressure; HF = heart failure; NYHA = New York heart association; PCI = percutaneous coronary intervention; CABG = coronary artery bypass surgery; ACE = angiotensin converting enzyme.

filling velocities of both ventricles was performed using the apical four-chamber view. Thus, the peak early diastolic filling velocity (E-wave), early diastolic deceleration time (DT), and peak late diastolic filling velocity (A-wave) were recorded. The systolic pulmonary artery systolic pressure (sPAP) was assessed by measuring the gradient between the right ventricle and the right atrium using the peak velocity (V_{max}) of the tricuspid regurgitation (sPAP = $4(V_{max})^2$ + right atrial pressure). The right atrial pressure was based on both the size of the inferior vena cava (IVC) and the change in diameter of this vessel during respiration.[13] Pulsed-wave Doppler recording of the hepatic vein flow was done using a sample volume placed in the hepatic vein 1 cm proximal to the junction of IVC and hepatic veins. Hepatic vein systolic/diastolic (S/D) ratio was calculated. For the right ventricle 2-D and TDI measurements, care was taken to obtain an ultrasound beam parallel to the tricuspid annulus motion. The RV endocardium was traced manually in systole and diastole. The RV fractional area change (RVFAC) was calculated using the formula: (end-diastolic area – end-systolic area)/end-diastolic area. Tricuspid annular plane systolic excursion was measured as recommended previously.[6] Tricuspid annular TDI was acquired in the apical 4-chamber view. Peak systolic (Sa_{tdi}), early diastolic, and late diastolic velocities of the tricuspid annulus were measured as recommended previously (sample TDI volume less than 5 mm and an angle between the TDI sample volume and the longitudinal myocardial wall vector less than 20°).[9] The ISW_{tdi} was measured with a minimized gain to obtain the maximal net border (Pictures 1–4).[10] Valvular regurgitation was graded according to guidelines of the American Society of Echocardiography.[14] All parameters were averaged over three heart cycles (five cycles for arrhythmia).

3.3. Clinical follow-up and endpoint definition

Clinical follow-up was for one year. The vital status of each patient was confirmed by a review of medical records or by telephone contact (family and/or patient). The primary endpoint was the combined risk of death or urgent heart transplantation or hospitalization for acute HF episode. Hospitalization for HF was defined as an admission for worsening HF in which intravenous therapy for HF was needed. The first event was considered for each patient.

3.4. Statistical analysis

The data were statistically analyzed using the Statistical Package for Social Sciences (SPSS) software version 17 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation and categorical variables as absolute numbers (percentages). Categorical variables were compared by Chi-square test. Continuous normally distributed variables were compared by two-tailed *t*-test. The optimal cut-off for the prediction of primary event was determined by a receiver-operator characteristic (ROC) curve. The area under the curve was the primary efficacy measurement. If the lower 95% CI of the area under the curve was > 0.5, we considered that the parameter may be suitable for a diagnostic

Table 2 Echocardiographic parameters of the patients according to the incidence of primary outcome events.

Variables	Event		
	Yes (n = 52)	No (n = 65)	p value
Left atrial diameter (mm)	48 ± 7	43.4 ± 3.9	0.0001
LV parameters			
LV end-diastolic dimension index (mm/m²)	36.7 ± 5	35.8 ± 5	> 0.05
LV end-systolic dimension index (mm/m²)	32 ± 5	30.2 ± 5	> 0.05
LV ejection fraction (%)	24.5 ± 5.4	31.4 ± 4.9	0.0001
Mitral early/late flow velocity	3.5 ± 1.4	2.5 ± 1.7	0.001
Mitral E/E′	14.2 + 5.2	13.4 + 6.5	> 0.05
Mitral deceleration time (ms)	130 ± 27	143.5 ± 39	0.04
Mitral TD systolic velocity (cm/s)	4.5 ± 1.4	5.2 ± 1.4	0.007
Mitral TD early diastolic velocity (cm/s)	7.1 ± 2.5	7.6 ± 3.3	> 0.05
Mitral TD late diastolic velocity (cm/s)	3.4 ± 1.2	4.8 ± 2.2	0.001
RV parameters			
RV end-diastolic area (cm²)	20.3 ± 6	15.9 ± 5	0.001
RV end-systolic area (cm²)	14.5 ± 5	9.9 ± 4	0.001
RV fractional area change (%)	30.1 ± 11	43.7 ± 6	0.025
Tricuspid plane systolic excursion (mm)	15.4 ± 4.1	17.5 ± 3.9	0.005
Tricuspid early/late flow velocity	1.2 ± 0.6	0.90 ± 0.4	0.03
Tricuspid TD systolic velocity (cm/s)	10.3 ± 1.7	12.9 ± 1.7	0.0001
Tricuspid TD integral of systolic wave (cm)	2.8 ± 1.5	3.4 ± 1.5	0.099
Tricuspid TD early diastolic velocity (cm/s)	10.5 ± 5	10.7 ± 3	0.01
Tricuspid TD late diastolic velocity (cm/s)	9.9 ± 4	12.6 ± 5	0.01
Pulmonary artery systolic pressure (mmHg)	51 ± 13	39 ± 10.5	0.001
Hepatic vein systolic/diastolic ratio	1.1 ± 0.5	1.4 ± 0.7	0.086

LV = left ventricle; E/E = early diastolic flow velocity/early diastolic annular TD velocity; TD = tissue Doppler. Data are expressed as a mean ± standard deviation or a number (percent).

test. ROC analysis was used to determine the sensitivity and specificity of RV echocardiographic parameters in predicting the primary endpoint. Logistic regression backward likelihood ratio technique was used to find out the significant independent predictors of the primary endpoint. A p value $\leqslant 0.05$ (2-tailed) was considered significant and a p value $\leqslant 0.01$ was considered highly significant. Reproducibility of RVFAC, TAPSE, ISW_{tdi} and Sa_{tdi} (intra-observer variability) was assessed by coefficient of variation for repeated measures in a random sample of 30 patients and was: 4%, 3%, 3%, and 1%, respectively.

4. Results

The study included 120 patients with chronic systolic HF and left ventricular ejection fraction (LVEF) <40%. Follow up was complete for 117 of 120 patients and the mean (SD) follow-up time was 318 ± 94 days. Fifty-two (44.4%) of 117 patients reached the primary endpoint (7 deaths, and 45 hospital admission for HF). The baseline demographic and clinical characteristics of the studied patients are detailed in Table 1. Patients with the primary outcome events had a higher

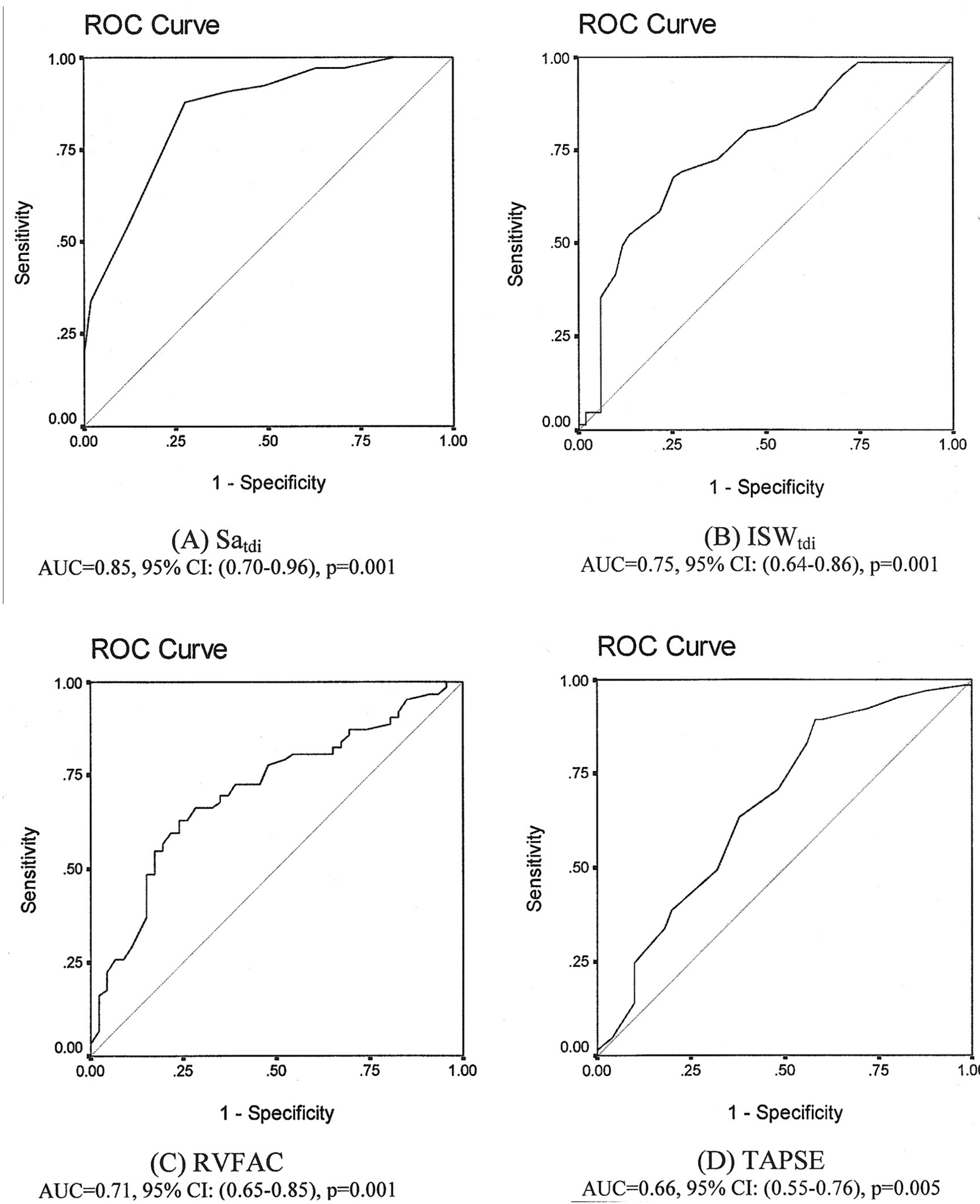


Figure 1 The receiver-operating characteristic curve for the primary endpoint (A) Sa_{tdi}, (B) ISW_{tdi}, (C) RVFAC, and (D) TAPSE. Sa_{tdi} = tricuspid TD integral of systolic wave; ISW_{tdi} = tricuspid TD integral of systolic wave; RVFAC = right ventricular fractional area change; TAPSE = tricuspid annular plane systolic excursion; AUC = area under the curve; CI = confidence interval.

Table 3 Diagnostic performance of different RV systolic parameters in prediction of primary events.

Variables	Best cut-off	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*p* value
Sa_{tdi} (in cm/s)	10	0.85(0.70–0.96)	92	65	75	93	0.001
ISW_{tdi} (in cm)	2.4	0.75(0.64–0.86)	80	55	58	85	0.001
RVFAC (%)	30	0.71(0.65–0.85)	72	63	67	82	0.001
TAPSE (in mm)	15.5	0.66(0.55–0.76)	75	55	63	80	0.005

AUC = area under the curve; CI = confidence interval; Sa_{tdi} = tricuspid annular TD peak systolic velocity; ISW_{tdi} = integral of tricuspid annular systolic wave; RVFAC = right ventricular fractional area change; TAPSE = tricuspid annular plane systolic excursion.

Table 4 Relation of all predictors to the event by logistic regression analysis.

Variables	Beta coefficient	Odd's (95% CI)	*p* value
NYHA class >2	0.98	2.1 (0.9–8.5)	<0.001
$Sa_{tdi} \leqslant 10$ cm/s	0.30	1.5 (0.2–6.95)	<0.05

CI = confidence interval; NYHA = New York Heart Association; Sa_{tdi} = Tricuspid annular TD peak systolic velocity.

incidence of advanced New York Heart Association (NYHA) class, diabetes, and past heart failure admission. They also used more diuretics, spironolactone, and digitalis.

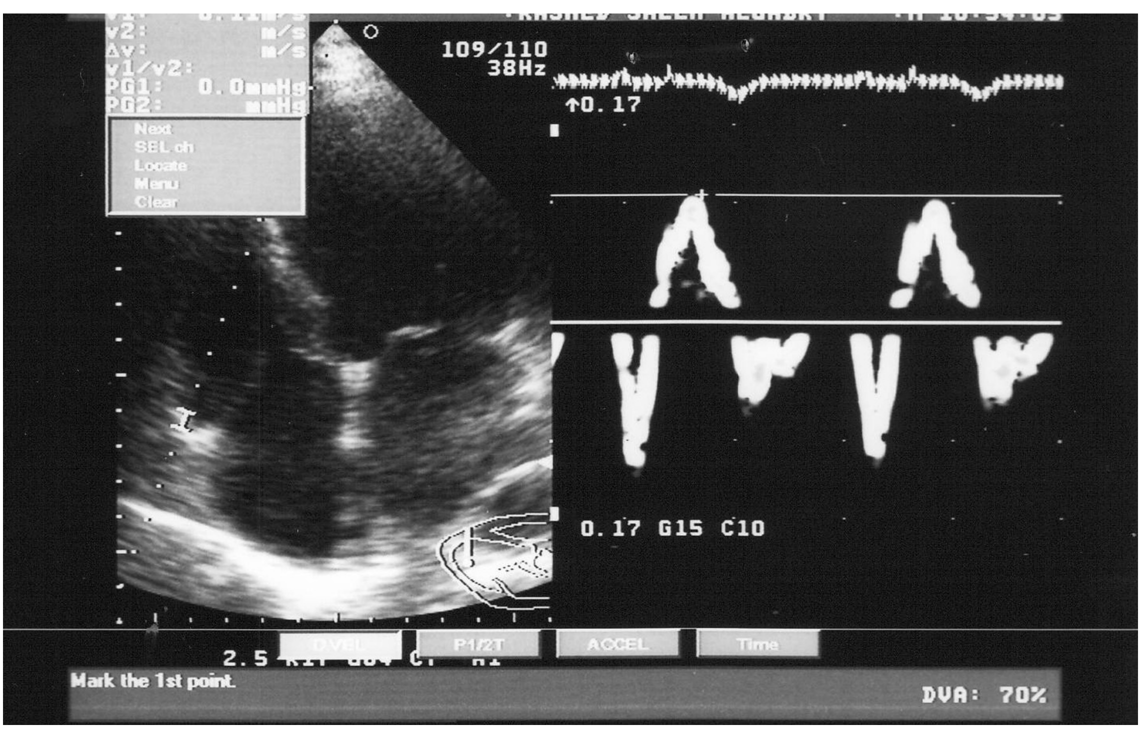
Echocardiographic variables in patients with and without an event are listed in Table 2. For left sided parameters, the group with outcome events showed significantly lower LVEF, mitral DT, mitral TDI systolic velocity, and mitral TDI late diastolic velocity, together with higher LA diameter, and mitral E/A ratio. For right-sided parameters, the group with primary endpoint events showed significantly lower RVFAC, lower TAPSE, and lower Sa_{tdi}. The ISW_{tdi} showed lower values with borderline significance.

4.1. Diagnostic performance of different RV systolic parameters in prediction of primary events

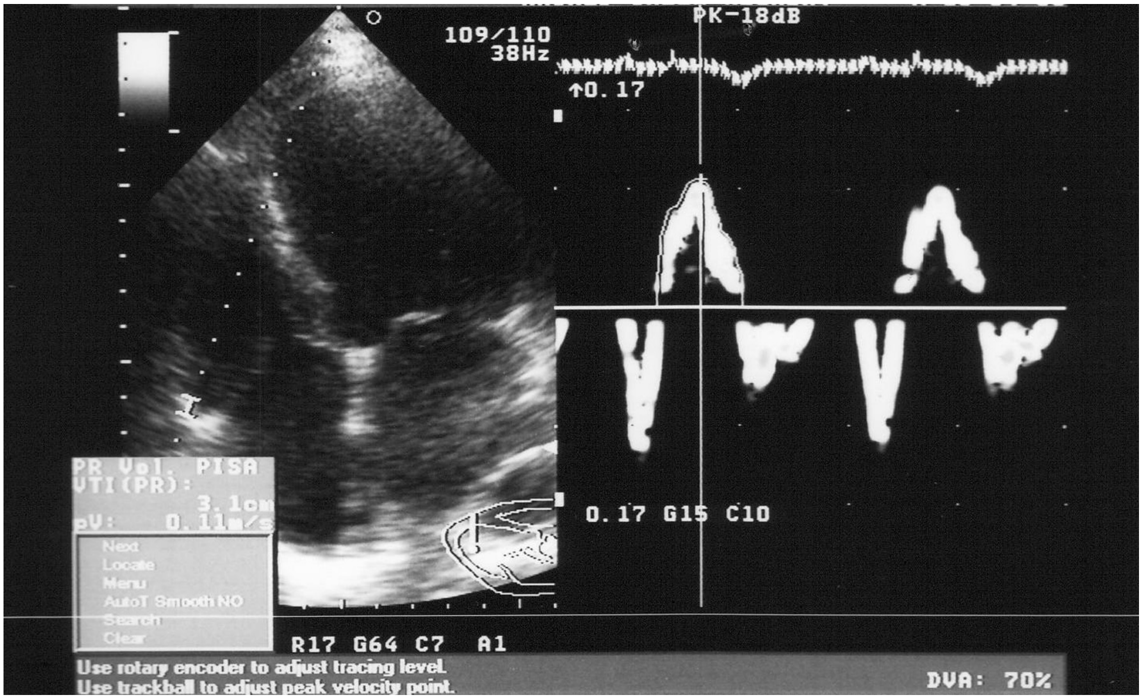
The ROC curves and the area under the curve for each RV systolic parameter are shown in Fig. 1. The four parameters were suitable for a diagnostic test as their ROC curve area was significantly greater than 0.50. The cut-off thresholds for Sa_{tdi}, ISW_{tdi}, RVFAC, and TAPSE to predict the primary endpoint were: 10 cm/s, 2.4 cm, 30%, and 15.5 mm, respectively (Table 3).

The Sa_{tdi} showed the highest diagnostic performance (area under the curve = 0.85, 95% confidence interval = 0.70–0.96, sensitivity = 92%, specificity = 65%, p = 0.0001). The overall mean Sa_{tdi} in the study population was 11.67 ± 2.13 cm/s. The mean Sa_{tdi} was lower in patients with an event than in those without an event (10.3 ± 1.7 vs. 12.9 ± 1.7, p = 0.0001).

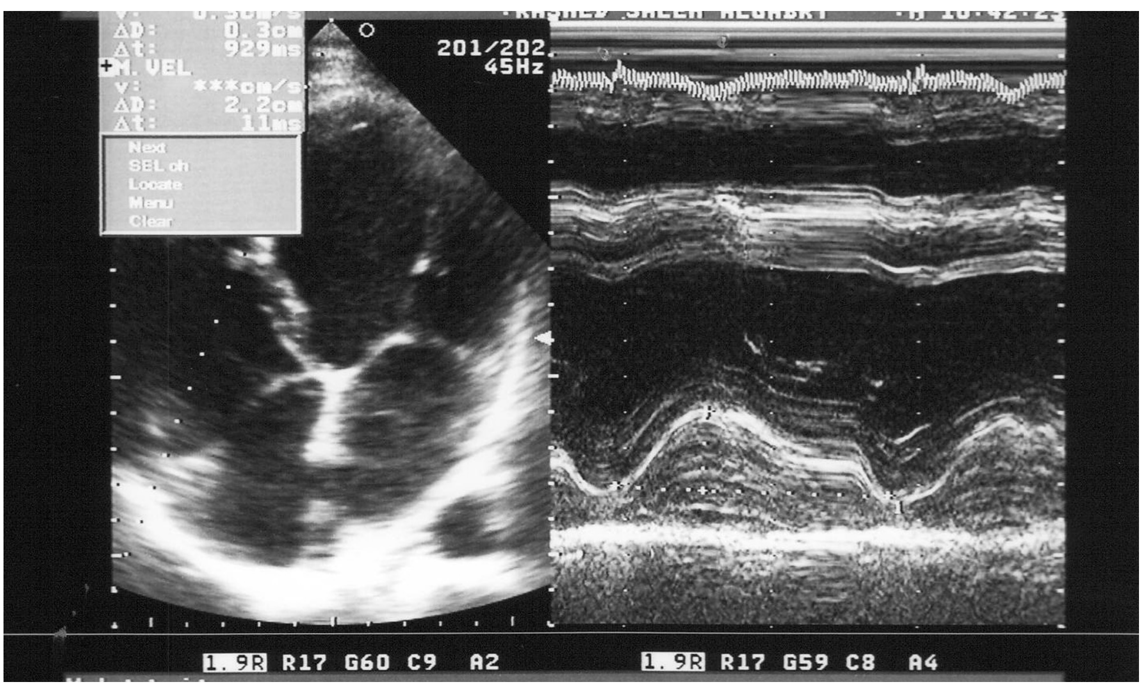
When all the significant variables were computed in a multivariate analysis, only NYHA functional class $>$II, and Sa_{tdi} remained independent predictors of adverse outcomes using logistic regression analysis (Table 4). Sa_{tdi} at a threshold of 10 cm/s was the only RV systolic parameter proved to be an independent predictor of outcome.



Picture 1 Measurement of tricuspid annular systolic wave (Sa_{tri}) with pulsed-wave tissue Doppler imaging, case 88.



Picture 2 Measurement of tricuspid annular integral of systolic wave (ISW_{tri}) with pulsed-wave tissue Doppler imaging, case 88.



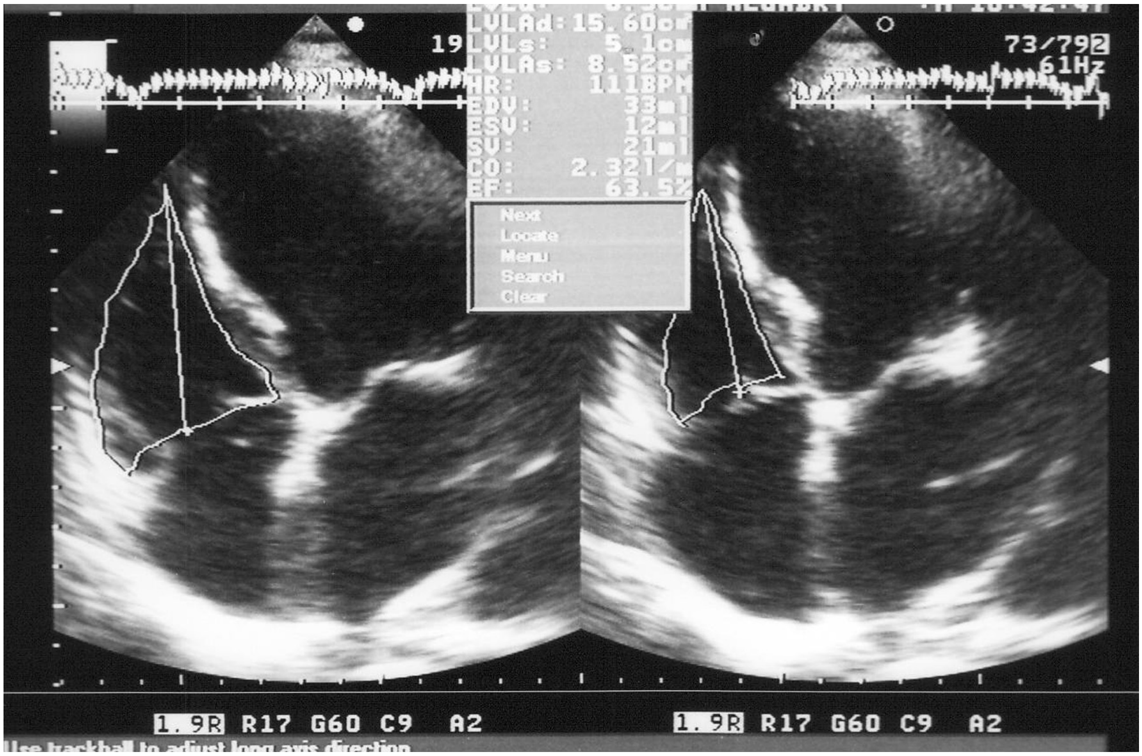
Picture 3 Measurement of tricuspid annular plane systolic excursion, case 88.

5. Discussion

In the present study, patients with systolic HF were followed for 1 year to determine the potential prognostic value of several RV systolic function parameters. Data analysis revealed that Sa_{tdi} is an independent predictor of outcome (death, urgent heart transplantation, or hospitalization for acute HF episode) in patients with chronic systolic HF with reduced LVEF, when other important markers such as NYHA and LVEF are considered. It also demonstrated that Sa_{tdi}, with a threshold value of 10 cm/s, is a better predictor of outcome than other RV systolic parameters (RVFA, TAPSE, and ISW_{tdi}).

5.1. Right ventricular dysfunction and prognosis in heart failure

RV systolic dysfunction is associated with poor long-term prognosis in patients with HF.[3,4] RVEF (assessed with thermodilution, or radionuclide ventriculography) predicts death,



Picture 4 Measurement of right ventricular fractional area change, case 88.

hospitalization and exercise capacity more accurately than the maximal oxygen consumption.[3–5] However, precise echocardiographic assessment of RV systolic function is challenging, primarily because the morphology of RV is complicated. Two-dimensional echocardiography assessing RV fractional area change is the mainstay for the analysis of RV function, but recently, alternative parameters have been suggested, including TAPSE, Sa_{tdi}, and ISW_{tdi}.

In the present study, Sa_{tdi} was shown to be an independent predictor of outcome. Damy et al.[15] studied 136 patients with stable HF and a left ventricular ejection fraction <35%, and demonstrated that Sa_{tdi} predicted of adverse outcome in HF at a threshold value of 9.5 cm/s. Similarly, Dokainish et al.[16] studied patients hospitalized with acute HF, and found that RV TD systolic velocity predicted cardiac death or rehospitalization for HF at a threshold value of 9 cm/s and appeared to be superior to conventional 2-dimensional parameters of RV function. Meluzin et al.[17] found that a Sa_{tdi} at a threshold of 10.8 cm/s represented a significant independent predictor of survival and event-free survival in patients with symptomatic heart failure. This higher threshold in the Meluzin study could be explained by the lower mean pulmonary artery pressure observed in their patients (28 ± 2 mmHg). Pulmonary artery pressure determines the RV afterload and is known to be associated with a worse RV function.[18]

5.2. Comparison of the prognostic ability of right ventricular echocardiographic parameters

The present study demonstrated that Sa_{tdi} is a better predictor of outcome than other RV systolic parameters. RVFAC, TAPSE, and ISW_{tdi} were correlated with the combined endpoint; however, they were not independent predictors of prognosis. Similarly, Damy et al.[15] demonstrated the superiority of Sa_{tdi} at a threshold value of 9.5 cm/s, compared with other echocardiographic indices of RV systolic function (RVFAC, TAPSE, and ISW_{tdi}), in predicting event-free survival in patients with chronic systolic HF. However, they studied patients one month after stabilization. In our study, we studied patients within 1 day of presentation whether they were stabilized or not. This may confer additional prognostic value to "stable" Sa_{tdi}. The rationale for this would be that a reduced "strained" Sa_{tdi} value would suggest that the RV is reaching the limit of its compensatory mechanisms.[19]

The reason why Sa_{tdi} was better than the other RV parameters is that it overcomes many of the limitations of the traditional methods of RV assessment. Despite involving the tricuspid annulus velocity, ISW_{tdi} was not an independent predictor of mortality. This result could be explained by a weaker correlation between ISW_{tdi} and the RVEF than Sa_{tdi} and the RVEF (r = 0.72, and 0.82, respectively).[10] In the present study, TAPSE had a lower diagnostic performance. This may result from the higher variability and difficulties in acquiring this measurement, compared with Sa_{tdi}. Damy et al. reported a lower sensitivity of TAPSE at a cutoff value of 13.5 mm, compared to Sa_{tdi}. A value of 14 mm for TAPSE was used by Ghio et al. to predict death or urgent transplantation.[20] However, this threshold was not obtained by ROC curve. This cut-off has subsequently been used in subsequent studies to determine the prognostic value of RV function.[21] The complex shape of the right ventricle may limit the measurement of RVFAC; the endocardial borders are often badly defined due to trabeculations and impede accurate calculation of the areas of the right ventricular cavity. Similar difficulties have been reported by other observers.[22,23]

5.3. Limitations of the study

The population studied was relatively small, but despite the sample size, there was a high event rate (44%). Therefore, we were able to reach several significant conclusions. We excluded patients with severe tricuspid regurgitation because the accuracy of the RV systolic parameter has not been established in such patients. Furthermore, we did not assess other RV parameters, such as the myocardial performance index and myocardial acceleration during isovolumic contraction, which are also correlated to RV dysfunction and HF prognosis.[24–27] Finally the present study did not include biological markers for adverse outcome in heart failure such as brain natriuretic peptide, but this would have increased the cost of the present study.

5.4. Conclusion and recommendations

Peak systolic velocity of the tricuspid annulus measured in tissue Doppler imaging is an independent predictor of adverse outcome in HF at a threshold value of 10.0 cm/s and appears to be superior to other RV systolic echocardiographic parameters.

In view of the small sample size included in this report, larger clinical studies are needed to confirm these observations. Future developments in the field of RV dysfunction in the setting of systolic HF may be directed toward assessment of other indices to accurately describe RV function, ideally being preload- and afterload-independent (such as myocardial acceleration during isovolumic contraction).

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Conflict of interest

Author declares that there is no conflict of interest.

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